

Original Article

Carvedilol, a Non-Selective β -with α_1 -Blocker is Effective in Long QT Syndrome Type 2

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Background: β -blockers offer the first line therapy in congenital long QT syndrome (LQTS), and are more effective to prevent the cardiac event in LQTS type 1 than in type 2 or 3. In contrast, left cardiac sympathetic denervation (LCSD) was shown to be highly effective in patients refractory to β -blockers. Total sympathetic ablation by LCSD indicates the additional involvement of α -adrenoceptor-mediated pathway. In genotyped LQT2 patients, we therefore hypothesized that blockade of α -adrenoceptor in addition to β -adrenoceptor by carvedilol could reduce cardiac events more efficiently than other types of β -blockers.

Methods and Results: The study population consisted of 51 genotyped LQT2 patients (18 males, 23 ± 11 years old). They were divided into 2 groups (group 1: 43 patients treated with selective β -blockers, group 2: 8 patients with carvedilol) and retrospectively analyzed the efficacy of the respective β -blocker therapy in suppressing cardiac events. Cardiac events were observed in 11 patients of group 1 (26%) but none in group 2 during a follow-up period of 83 ± 80 months ($P = 0.098$).

Conclusions: Carvedilol may be a potentially beneficial therapy for genotyped LQT2 patients who are refractory to other β selective blockers.
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Key words: Long QT syndrome, β -blocker therapy, carvedilol, α -adrenoceptor

Introduction

Long QT syndromes (LQTS) are heterogeneous inherited ion channelopathies characterized by pro-

longed ventricular repolarization, syncope, ventricular arrhythmias, and sudden cardiac death with normal cardiac structure.¹⁾ Sympathetic activation and arrhythmogenesis are uniquely associated with

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LQTS. For example, in LQTS type 1 (LQT1), exercise produces the QT prolongation and subsequent arrhythmic episodes.^{2,3)} β -blockers are therefore routinely prescribed in symptomatic LQT1 patients and reported to prevent first cardiac events in 74–80% of patients.^{4,5)} In contrast, in LQT2, cardiac symptoms mainly develop at rest, while sleeping or by auditory stimuli,⁶⁾ and the efficacy of β -blockers is limited compared to that in LQT1. In a recent report⁷⁾ with large cohort of LQT2, β -blocker use reduced the risk of first cardiac events by 63%, however it was associated with less protection (29%) in the prevention of lethal cardiac events.

As to the additional therapy for patients refractory to β -blockers, left cardiac sympathetic denervation (LCSD) has been shown to be highly effective.^{8,9)} Total sympathetic ablation by LCSD indicates the additional involvement of α -adrenoceptor-mediated pathway. Labetalol, an α_1 - and non selective β -blocker, was reported to be effective to suppress cardiac events in LQTS, although patients in this study were not genotyped.¹⁰⁾ As an anecdotal case, we experienced that a LQT2 patient (S871fs+31X) whose repetitive syncope due to TdP was not suppressed by propranolol (30 mg per day), but subsequent carvedilol (10 mg per day), an α_1 - and non selective β -blocker, was fully effective.

Indeed, the difference in response to β -blockers may result from the distinct sympathetic response of I_{Ks} currents (encoded by *KCNQ1* gene that underlines LQT1^{11,12)}) and I_{Kr} currents (encoded by *KCNH2* gene that underlines LQT2¹³⁾), which are both critically responsible for ventricular repolarization. We recently demonstrated both in CHO cells and HL-1 cardiomyocytes that Kv 11.1 channels encoded by *KCNH2* are acutely downregulated

by α_1 -adrenergic stimulation.¹⁴⁾ In the presence of reduced function with Kv11.1 mutants (Y43D and K595E), additional α_1 -adrenergic stimulation led to a further decrease in residual channel currents and thereby producing an extreme delay in repolarization. Thus, α_1 -adrenoceptor blockade might serve as a promising medication and improve the symptoms in LQT2 patients. We therefore retrospectively surveyed the efficacy of carvedilol for suppressing cardiac events compared to other β -selective blockers in genotyped LQT2 patients.

Methods

Study population (Figure 1) and genetic analysis

The study cohort consisted of 82 LQT2 probands and their 51 family members, who were referred as inherited cardiac arrhythmia subjects from 36 institutes in Japan, and genotyped from June 1996 to December 2009 in Shiga University of Medical Science (Otsu) or Kyoto University Graduate School of Medicine (Kyoto). The patients with LQT1, 3, 5, 6, 7 or compound mutations¹⁵⁾ were excluded. In the total of 133 LQT2 patients, the β -blocker therapy was introduced in 51 patients, which consisted of our final study population (Figure 1).

DNA sequence analyses of *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ2* were performed as described previously.^{16,17)} Mutation screening was performed using polymerase chain reaction (PCR) or denatured high-performance liquid chromatography analyses (dHPLC, WAVE system; Transgenomic Inc., Omaha, NE, USA).¹⁸⁾ For aberrant PCR products, DNA sequencing was then conducted with a DNA sequencer (ABI 3130 DNA Sequencer; Perkin Elmer, Foster City, CA, USA). When a mutation was detected, the result was

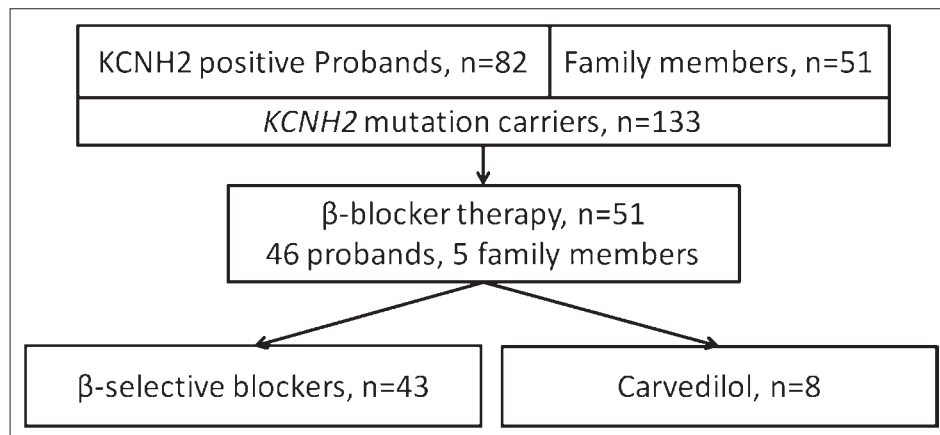


Figure 1 Schematic representation of the positive-mutation carriers in this study.

compared to >200 Japanese control subjects, and single nucleotide polymorphisms were excluded from this study.

The protocol for genetic analysis complied with the Declaration of Helsinki and was approved by the institutional ethics committees and performed under their guidelines. All individuals or their guardians gave written informed consent to genetic and clinical data analyses.

Clinical characteristics

In 51 LQT2 patients receiving the β -blocker therapy, baseline clinical characteristics were collected including age at diagnosis, age at the first cardiac event, age at β -blocker therapy started, and Schwartz score.¹⁹⁾ With regard to family history, we defined it as positive if a subject had a family member who had Schwartz score of ≥ 4 . Triggers of symptom were defined as follows: 1) at rest/during sleep, 2) arousal, 3) auditory stimuli, 4) pregnancy/post delivery and 5) during exercise.

ECG parameters used for analyses were baseline heart rate (HR) and QT intervals. Measurements were performed in 3 successive sinus beats in lead II (if not possible, in lead V5) and averaged. QT was manually measured as the time interval between QRS onset (Q) and the point at which the isoelectric line intersected a tangential line drawn at the maximal down slope of the positive T wave or the upslope of the negative T wave (QT), and corrected using Bazett's formula.²⁰⁾

LQTS-related cardiac events included unexplained syncope, aborted cardiac arrest requiring cardiac resuscitation, appropriate ICD shock and unexpected sudden death exclusive of a known cause before age 45 years. Those data were compared between the group treated with β -selective blockers and the group with carvedilol.

Treatment including β -blocker therapy

The specific β -blocker used, as well as dose, was at the discretion of the treating physician. The type and dose of β -blocker used, cardiac event rate on each β -blocker, adjunctive therapy and follow-up period were collected and compared between the β -selective blockers group and the carvedilol group. If patients were treated with β -selective blockers and thereafter carvedilol due to ineffective β -blocker therapy, they were included in the carvedilol group. Follow-up period was calculated from the starting date of β -blocker to the day of a cardiac event. We excluded patients from analysis who were non-compliant to a prescribed β -blocker.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD) for continuous variables. Comparisons were performed by chi-square test for categorical variables and *t*-test for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first event and the cumulative event rates by groups were compared using the log-rank test. $P < 0.05$ was considered statistically significant. The statistical software used for the analyses was JMP version 7.0.1 (SAS institute Inc., NC, USA).

Results

Characteristics of the study population

In our LQTS cohort, 133 patients from 82 unrelated families were identified as sole *KCNH2* mutation carriers. In those LQT2 patients, 51 patients (46 probands and 5 family members) received the β -blocker therapy. To compare the clinical characteristics, we divided the study population into 2 groups: the β -selective blockers group (43 patients, mean age at diagnosis 22 ± 11 years) and the carvedilol group (8 patients, mean age at diagnosis 26 ± 11 years) (**Figure 1**).

Table 1 shows the clinical characteristics of the two groups. Regarding triggers of symptoms, sudden arousal was more frequent in the carvedilol group ($P = 0.0313$). There was no statistical difference between the two groups including age, gender, Schwartz scores, ECG parameters and cardiac events before therapy. Distribution of mutations was not significantly different between the two groups.

Treatment

As an adjunctive therapy, β -selective group received mexiletine more frequently than the carvedilol group (10/43 β -selective group vs. 0/8 carvedilol group, $P = 0.0473$) (**Table 1**). Ten patients (9/43 in the β -selective group, 1/8 in the carvedilol group) were implanted with an implantable cardioverter defibrillator (ICD). No patients underwent LCSD.

β -Blocker therapy (**Table 2**)

The β -blocker therapy was started at age of 19 ± 12 (0–63) years in total, 17 ± 11 years in the β -selective group and 26 ± 12 years in the carvedilol group, respectively (**Table 1**). The mean age of carvedilol start was significantly ($P = 0.0372$) older than that of β -selective blockers. We experienced three patients in whom β -selective blockers first failed but subsequent carvedilol was successful to prevent cardiac events. Those cases were included

Table 1 Clinical characteristics

	All patients n = 51	β -selective blockers n = 43	Carvedilol n = 8	P value
Demographics				
Proband, n (%)	46 (90)	40 (93)	6 (75)	N.S.
Male, n (%)	18 (35)	16 (37)	2 (25)	N.S.
Age at diagnosis, mean \pm SD, years	23 \pm 11	22 \pm 11	26 \pm 12	N.S.
Age at first cardiac event, mean \pm SD, years	15 \pm 10	14 \pm 9	18 \pm 10	N.S.
Age at β -blocker started	19 \pm 12	17 \pm 11	26 \pm 12	0.0372*
Schwartz score, mean \pm SD	5.2 \pm 1.7	5.2 \pm 1.7	5.6 \pm 1.3	N.S.
Electrocardiogram				
HR, mean \pm SD, bpm	63 \pm 10	61 \pm 7	64 \pm 11	N.S.
QTc, mean \pm SD, ms	515 \pm 63	513 \pm 62	525 \pm 65	N.S.
Location of mutation, n (%)				
N terminal	10 (17)	8 (17)	2 (25)	N.S.
C terminal	18 (35)	16 (37)	2 (25)	N.S.
Pore	11 (22)	10 (23)	1 (13)	N.S.
Trans membrane	12 (24)	9 (21)	3 (38)	N.S.
Non-missense mutation, n (%)	22 (43)	17 (40)	5 (62)	N.S.
Cardiac events before β-blocker therapy				
Syncope, presyncope, n (%)	48 (94)	40 (93)	8 (100)	N.S.
Documented TdP, n (%)	26 (51)	22 (51)	4 (50)	N.S.
Documented VF, n (%)	5 (10)	5 (12)	0 (0)	N.S.
Trigger of symptoms				
At rest, during sleep, n (%)	24 (50)	22 (55)	2 (25)	N.S.
Arousal, n (%)	10 (20)	6 (15)	4 (50)	0.0313*
Auditory stimuli, n (%)	7 (14)	6 (15)	1 (12)	N.S.
Pregnancy, post delivery, n (%)	3 (6)	2 (5)	1 (13)	N.S.
Exercise, n (%)	2 (4)	2 (5)	0 (0)	N.S.
Adjunctive LQTS therapy (any time)				
Mexiletine, n (%)	10 (20)	10 (23)	0 (0)	0.0473*
Pacemaker, n (%)	0	0	0	N.S.
LCSD, n (%)	0	0	0	N.S.
ICD, n (%)	10 (20)	9 (21)	1 (13)	N.S.
Follow-up duration after β -blocker, month \pm SD	83 \pm 80	84 \pm 86	73 \pm 43	N.S.

*P < 0.05 vs β -selective blocker group

TdP: Torsade de pointes, VF: ventricular fibrillation, LCSD: left cardiac sympathetic denervation, ICD: implantable cardioverter defibrillator

into the carvedilol group because they recurred shortly after β -selective blocker treatment and the period for carvedilol therapy was sufficiently long. β -selective blockers used in 43 LQT2 patients were atenolol in 7 patients (75.0 ± 61.2 mg, 25–200 mg), bisoprolol in 3 (4.2 ± 1.2 mg, 2.5–5.0 mg), carteolol in 1 (20 mg), metoprolol in 5 (68.0 ± 33.1 mg, 30–120 mg), nadolol in 1 (60 mg), and propranolol in 26 (34.0 ± 13.3 mg, 10–60 mg). Eight patients were treated with carvedilol (16.9 ± 10.3 mg, 5–40 mg). Unfortunately, we have no data of patients' body weight, and the data of mg per kg were not shown.

Cardiac events during follow-up

Mean follow-up durations without any cardiac events after drug introduction were 84 ± 86 months in the β -selective blocker group and 73 ± 43 months in the carvedilol group. Eleven patients (26%) had cardiac events while receiving β -blocker therapy, but no one (0%) experienced arrhythmic episodes in the carvedilol group (Table 3). Kaplan-Meier survival curve showed a tendency of superior efficacy of carvedilol ($P = 0.098$, log-rank test) (Figure 2). Three of 11 recurrence cases had pore mutations (27%), and four had non-missense mutations (36%),

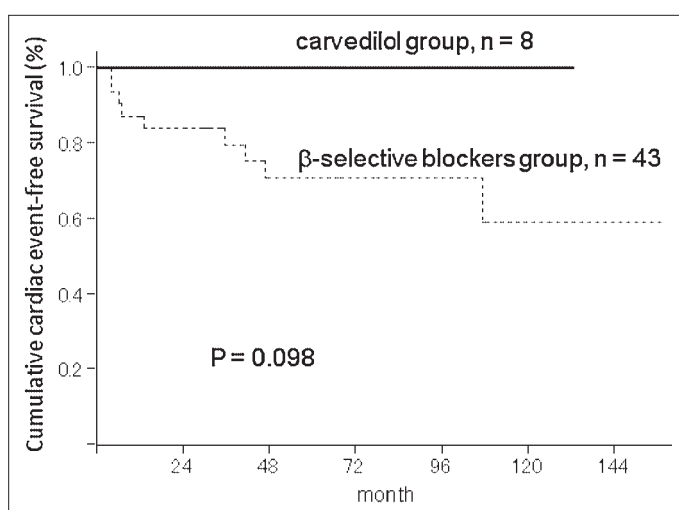
Table 2 Dose and variety of β -blockers

	n, (%)	Dose per day, mean \pm SD (range)
β-selective blockers, n = 43		
Atenolol	7 (14)	75.0 \pm 61.2 (25–200) mg
Bisoprolol	3 (6)	4.2 \pm 1.2 (2.5–5) mg
Carteolol	1 (2)	20 \pm 0 mg
Metoprolol	5 (10)	68.0 \pm 33.1 (30–120) mg
Nadolol	1 (2)	60 \pm 0 mg
Propranolol	26 (51)	34.0 \pm 13.3 (10–60) mg
Non-selective β- and α_1-blocker, n = 8		
Carvedilol	8 (16)	16.9 \pm 10.3 (5–40) mg

Table 3 Cardiac events on β -blocker therapy

	β -selective blocker, n = 43	Carvedilol n = 8
Total of cardiac events, pt n, (%)	11 (26)	0
Syncope, n, (%)	11 (26)	0
Documented TdP, n, (%)	4 (9)	0
Aborted sudden cardiac arrest, n, (%)	1 (2)	0
Appropriate ICD shock, n, (%)	2 (5)	0

TdP: Torsade de pointes, ICD: implantable cardioverter defibrillator

**Figure 2** Kaplan-Meier analysis of cumulative cardiac event-free survival from each β -blocker therapy started to 150 months.

and therefore these incidences were not significantly different irrespective of β -selective blocker effectiveness.

Two of eleven patients (18%) in the β -selective blocker group experienced appropriate ICD shocks: one patient treated with propranolol (30 mg per day) and another treated by nadolol (60 mg per day), who showed an electrical storm. In two patients with ineffective propranolol therapy, recurrent syncope was controlled by diazepam as an adjunctive therapy.

Three of eight patients in the carvedilol group were first treated with propranolol, but experienced recurrent cardiac events, and the treatment was changed to carvedilol. In two cases, carvedilol was introduced because it was longer acting than propranolol. In the one remaining case, carvedilol was prescribed because of its additional α -blocking action.

Figure 3A shows a family tree showing a typical case that was refractory to propranolol but success-

fully controlled by carvedilol. The proband was a 9-year-old girl (indicated by arrow in **Figure 3A**), and genetic test identified a heterozygous *KCNH2* mutation (S871fs+31X). She was diagnosed as long QT syndrome at age of 6 years (12-lead ECG in **Figure 3B**, QTc = 500 ms) but remained asymptomatic. At age 9, she had loss of consciousness twice just after waking to an alarm clock in the morning. Her Holter ECG (**Figure 3C**) revealed repetitive TdP triggered by auditory stimuli, and she complained of uncomfortable chest distress. Propranolol (30 mg per day) was then prescribed, but her clinical complaints continued. Medication was finally switched to carvedilol (10 mg per day), which completely relieved her symptoms though the drug did not alter her QTc and HR. Her mother also collapsed at the delivery of the proband at age of 32 and genetic test revealed the same *KCNH2* mutation. Carvedilol was also started to prescribe for this proband's mother.

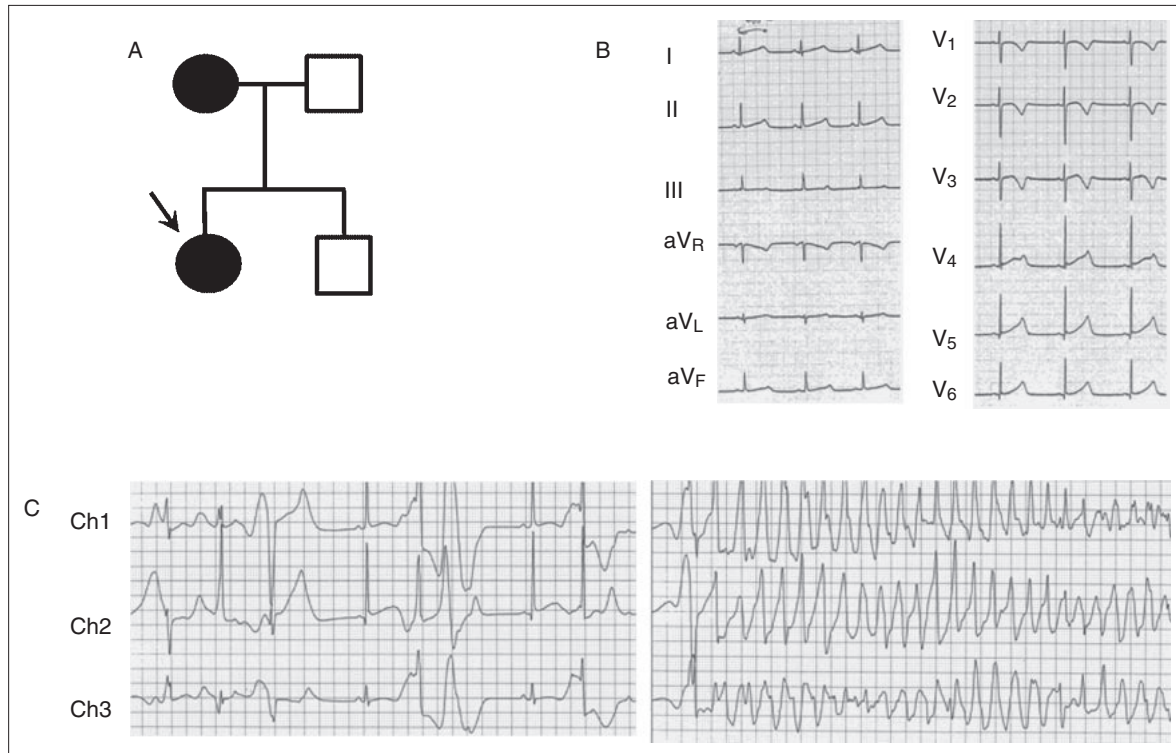


Figure 3 A typical case that was refractory to propranolol but controlled by carvedilol.

A. A pedigree of *KCNH2*-S871fs+31X. Circle indicates female, square indicates male. Closed symbol indicates mutation positive subject. Black arrow indicates proband of this family, a 9-year-old girl. **B.** 12 lead ECG at resting state of proband. QTc = 500 msec (V5). **C.** A Holter ECG of proband. TdP was detected during an episode of syncope triggered by alarm clock early in the morning. Left panel: just before the TdP. Right panel: TdP following left panel.

Discussion

In our study cohort of LQT2 patients, carvedilol, which blocks both α_1 - and β -adrenoceptors, was more effective than other β -selective blockers in suppressing cardiac events without major complications. As widely recognized, β -blockers are the first line therapy for the prevention of cardiac events in the long QT syndrome. The studies on genotype-phenotype relationships of the syndrome in the last decade, however, have confirmed that β -blockers are most effective in LQT1, but less in LQT2 or LQT3 patients.⁴⁾ For example in 2004, Priori and colleagues²¹⁾ reported nearly a 3-fold increase in the risk of cardiac events during β -blocker treatment in LQT2 as compared to LQT1 patients, although there is a conflicting report by Goldenberg and colleagues.²²⁾ They demonstrated that a β -blocker was sufficiently effective in high risk patients with both LQT1 and LQT2. As to α_1 - and β -blockers, there are a few reports which demonstrated that α_1 - and β -adrenoceptor blockade was effective to shorten QTc interval in the upright position before exercise and early recovery phase after exercise,²³⁾ or suppress

arrhythmic events in LQTS with unknown genotype.¹⁰⁾ There is another suggestive study of Khositseth et al.²⁴⁾ that phenylephrine-induced bradycardia increased transmural dispersion of repolarization (TDR) in symptomatic LQT2 but not in LQT1 patients. Therefore, α_1 -adrenoceptor blockade (in addition to β -adrenoceptor blockade) in LQT2 patients may actually lead to suppression of QT prolongation and/or TDR, and eventually TdP. The results in the present study were in line with the above-mentioned hypothesis, and carvedilol actually appeared to be beneficial in suppressing cardiac events in LQT2.

As Moss et al. reported in 1971,²⁵⁾ LCSD offers an alternative therapy to block sympathetic activation for LQTS patients without reducing heart rate. Antiarrhythmic action of LCSD is due largely to the electrophysiological consequences of reduced release of norepinephrine at the ventricular level and includes prevention/suppression of early afterdepolarization (EAD). Although it does not entirely control all cardiac events, the operation significantly reduces the number of symptoms and ICD shocks.⁹⁾ As the LCSD suppresses both β - and α -adrenergic

contribution of sympathetic control, blockade of α_1 -adrenoceptors in addition to β -adrenoceptors by medication would also be useful to suppress the severe form of cardiac events.

More recently, we reported that α_1 -adrenergic stimulation acutely reduced Kv 11.1 channel activities via membrane PIP₂ pathway.¹⁴⁾ Sudden α_1 -adrenoceptor-mediated reduction in I_{Kr} at a lower HR (for example, during sleep) would act additionally to prolong action potential durations and may enhance inward current through Na/Ca exchanger, both contributing to the occurrence of EAD.²⁶⁾ These observations may partially explain why sudden auditory stimulation by an alarm clock induces cardiac events in LQT2 patients.⁶⁾ In this connection, more recently Kim and colleagues²⁷⁾ demonstrated in a large cohort of genotyped LQT2 patients that β -blockers were less effective in patients with arousal or non-exercise triggered events than those with exercise triggered events to prevent the recurrence. Although they did not mention the detailed species of β -blockers used for their patients, in our cohort, 11 recurrence cases in spite of β -selective blockers were all triggered by arousal or in a non-exercise resting state, and carvedilol prevented the cardiac event in three who were initially refractory to propranolol.

Study limitations

Because this study was conducted in a retrospective manner, we were not able to adjust the selection of patients between the two groups. Our study cohort consisted of a relatively small number of LQT2 patients. In the carvedilol group, there were no recurrent cases, which made further statistical analyses, such as multivariate correlation study, difficult. A further study with a larger number of patients will be awaited. In conclusion, in our genotyped LQT2 cohort, carvedilol was effective to suppress cardiac events, whereas 26% of the patients treated with other β -selective blockers experienced cardiac events, suggesting that the simultaneous blockade of α_1 -adrenoceptors may offer an additional therapy for LQT2 patient with non-exercise triggers.

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